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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,978	BUDAHAZI ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-47* is/are rejected.

7)☒ Claim(s) *46 and 47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed July 23, 2009. Claims 1-40 were previously pending, with claims 1-20 withdrawn from consideration. Applicants cancelled claims 21-40 and added new claims 41-47. Claims 41-47 are pending and will be examined.

2. Applicants' claim cancellations overcame all of the previously presented rejections. This office action contains new grounds for rejection necessitated by amendment.

Claim Objections

3. Claims 46 and 47 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 46 is drawn to the DNA product of claim 41, wherein the DNA product is essentially free of host cell derived pathogens, and claim 47 drawn to the DNA product of claim 41, wherein the DNA product is essentially free of host chromosomal DNA. Claim 41 lists specific numerical ranges for the amount of endotoxins and host chromosomal DNA. Applicants did not define what it means, in terms of numerical values, for the product to be "essentially free" of these components, therefore these claims do not further limit claim 41.

Claim Rejections - 35 USC § 112, new matter

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 41-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following limitation of claim 41 does not have support in the specification or in the originally filed claims: "weight range of RNA is less than 0.0001% to 0.00001% RNA".

The specification discloses, on pages 19 and 20, paragraphs [0068] and [0069], the following RNA concentrations: "less than about 5% by weight of RNA, such as, e.g., about 5% by weight of RNA to about 0.00001%, or less than 0.0001%", " less than about 5% by weight of RNA". Therefore there is no support for the claimed range of RNA concentration in the originally filed disclosure.

In conclusion, the above listed limitation of claims 41 introduces new matter into the claims.

Claim Rejections - 35 USC § 112, written description

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 41-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 41 is drawn to a DNA product comprising from about 95% to about 100% of circular plasmid DNA, wherein said DNA product contains

less than 5% by weight of RNA wherein said weight range of RNA is less than 0.0001% to 0.00001% RNA;

a weight range of host DNA from less than 0.002 μg to 0.00002 μg of host DNA/μg of DNA product;

a weight range of protein from about 0.00000001 μg to about 0.001 μg protein per μg DNA product;

an endotoxin amount ranging from 0.0001 EU/μg to 0.0002 EU/μg of DNA product;

and wherein said DNA product contains an amount of host cell derived impurities that is undetectable under normal assay conditions by any one of a group consisting of: LAL assay, Southern blot assay, chromatography, Northern blot assay, and ethidium bromide agarose analysis.

However, there is no support in the specification or claims as originally filed for the claimed product. The specification discloses, on pages 19 and 20, paragraphs [0068] and [0069], the following DNA products:

"The DNA product obtained by the process of the invention can comprise about 95% or greater by weight of circular plasmid DNA, wherein said DNA product contains less than about 5% by weight of RNA, less than about 0.002 μg of host DNA/μg of DNA product, less than about 0.001 μg of protein/μg of DNA product, and less than about 0.01 EU/μg of DNA product."

The following plasmid DNA products were obtained by Applicants in the Examples:

A) Example 1: DNA product with 0.0004 μg of host DNA/μg of DNA product and 0.0002 EU/μg of DNA product. No RNA or protein levels were specified. No percentage of circular plasmid DNA was specified.

B) Example 2: DNA product with 0.00025 μg of host DNA/μg of DNA product and 0.0002 EU/μg of DNA product. No RNA or protein levels were specified. No percentage of circular plasmid DNA was specified.

C) Example 3: DNA product with 0.00029 μg of host DNA/μg of DNA product and 0.00001 EU/μg of DNA product. No RNA or protein levels were specified. No percentage of circular plasmid DNA was specified.

D) Example 4: DNA product with 0.001 μg of host DNA/μg of DNA product and 0.0006 EU/μg of DNA product. No RNA or protein levels were specified. No percentage of circular plasmid DNA was specified.

E) Example 5: DNA product with 0.0002 μg of host DNA/μg of DNA product and 0.00019 EU/μg of DNA product, with 92% of supercoiled DNA. No RNA or protein levels were specified. The average of four purifications resulted in DNA product with 0.0005 μg of host DNA/μg of DNA product and 0.0001 EU/μg of DNA product, with 90% of supercoiled DNA. No RNA or protein levels were specified.

The original claim 30 read as follows:

"A DNA product comprising about 95% or greater by weight of circular plasmid DNA, wherein said DNA product contains less than about 5% by weight of RNA, less than about 0.002 μg of host DNA/μg of DNA product, less than about 0.001 μg of protein/μg of DNA product, and less than about 0.01 EU/μg of DNA product."

Therefore taking into account the original disclosure as well as the experimental examples, there is no evidence that Applicants were in possession of the DNA products as claimed in claims 41-47, especially with respect to the degree of RNA and protein removal.

Claim Rejections - 35 USC § 112, second paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 41-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 41-47 are indefinite in claim 41. Claim 41 is indefinite over the recitation of "wherein said DNA product contains an amount of host cell derived impurities that is undetectable under normal assay conditions by any one of a group consisting of: LAL assay, Southern blot assay, chromatography, Northern blot assay, and ethidium bromide agarose analysis." (lines 11-13).

It is not clear what are the meets and bounds of these limitations. Lines 3-10 of the claim list specific weight percentages of the following impurities: RNA, host DNA, host protein and endotoxin. Applicants did not show that the value ranges listed in lines 3-10 of the claim are undetectable by any one of these techniques, or provided ranges which are undetectable. Therefore lines 3-10 seem to contradict the limitation of lines 11-13. Further, the detection limit of any particular assay depends on the conditions under which it is performed as well as the ingredients used, the level of impurities detected will depend on where and how the assay is performed. Applicants did not specify conditions and cutoff values for any of these assays which would result in undetectable levels of impurities, or what it means for the assay to be performed under "normal conditions".

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 41-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nochumson et al. (US 2001/0034435 A1; cited in the IDS and in the previous office action), Marquet et al. (WO 95/21250; cited in the IDS and in the previous office action), Kvederas et al. (US 2003/0109696 A1; cited in the previous office action), Cooke et al. (J. Biotechnol., vol. 85, pp. 297-304, February 2001; cited in the previous office action), Lee et al.(WO 96/02658; cited in the IDS and in the previous office action) and Lander et al. (WO 01/46215; cited in the IDS and in the previous office action).

A) Regarding claims 41, 46 and 47, Nochumson et al. teach plasmid DNA and pharmaceutical preparation (page 8, [0099]). Nochumson et al. teach plasmid DNA preparation with 95% plasmid DNA and less than 5% RNA (page 8, [0099]). Nochumson et al. teach plasmid DNA preparation with 0.05% of host DNA (page 8, [0099]), which is equivalent to 0.0005 μg of host DNA/μg of DNA product, therefore Nochumson et al. anticipate the range from 0.00002 to 0.002 μg of host DNA/μg of DNA product. Nochumson et al. teach plasmid DNA preparation with less than 0.06% of protein (page 8, [0099]), which is equivalent to 0.0006 μg of protein/μg of DNA product, therefore Nochumson et al. anticipate the range from about 0.00000001 to about 0.001 μg of protein/μg of DNA product (claims 21, 22, 40). Nochumson et al. teach plasmid DNA

preparation with less than 0.2EU/mg of endotoxin, which equals less than 0.0002 EU/μg of DNA product (page 8, [0099]), anticipating the range from about 0.0001 EU to 0.0002 EU/μg of DNA product. Considering the ranges of impurities presented by Nochumson et al., their plasmid preparations are essentially free of endotoxins and chromosomal host DNA.

Regarding claims 43-45, Nochumson et al. teach pharmaceutical preparations (claims 8, 11, 19, 31).

Regarding claim 42, Nochumson et al. teach sterile preparations (page 7, [0079].

Nochumson et al. do not specifically teach that any of these contaminant levels are undetectable under normal assay conditions by any one of the following: LAL assay, Southern blot assay, chromatography, Northern blot assay, and ethidium bromide agarose analysis.

Marquet et al. teach plasmid DNA and pharmaceutical preparation (page 30-32), where the levels of RNA, host protein, endotoxin and host DNA are undetectable by gel electrophoresis, BCA analysis, LAL analysis and Southern blot, respectively, and where the preparation is free of pyrogens (page 31, Table). As can be seen from Table on page 31, the detection limit of endotoxin by LAL assay corresponds to 0.1 EU/μg of DNA, therefore the amount of endotoxin present in the preparation of Nochumson et al. would have been undetectable by the LAL assay.

Regarding claims 42-45, Marquet et al. teach pharmaceutical preparations and sterile containers (page 2, lines 24-25; page 3, lines 21-24; page 4, lines 17-19; page 15, lines 28-31; page 16, lines 1-3).

B) Nochumson et al. do not teach RNA contaminant levels from about 0.00001% to about 0.0001% or 0.00004 μg of host DNA/μg of DNA product.

C) The references cited below show that different levels of impurities in plasmid DNA can be obtained depending on the type of purification method used. Kvederas et al. teach a method of

plasmid DNA purification from bacterial cells which results in a removal of bacterial RNA from the preparation to undetectable levels (Abstract; page 14, 15, Tables 3 and 4). Other impurity levels were as follows (Table 3): 0.035 EU//μg of DNA product and 0.000000346 μg of host protein/μg of DNA product.

Cooke et al. teach removal of RNA from plasmid preparations using host cells expressing a ribonuclease (Abstract; page 299, second paragraph).

Lee et al. teach a plasmid preparation with 0.029 μg of host DNA/μg of DNA product, less than 0.01 μg of protein/μg of DNA product, less than 0.01% RNA and 0.0028 EU/μg of DNA product (page 17, Table 1). Lander et al. teach a plasmid DNA product with undetectable protein content, 0.00003 EU/μg of DNA product EU/μg of DNA product and 0.043% RNA (Table 4, page 35).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have further purified the plasmid of Nochumson et al. to achieve the desired impurity levels, since, as indicated by the cited references, the level of impurities obtained depended on the purification method, and thus could be achieved by routine optimization. It would have been prima facie obvious to perform routine optimization using reagents and purification procedures, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection specific contamination levels was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in

any way as compared to the closest prior art.

The motivation to remove RNA to undetectable levels was provided by Kvederas et al. (page 1, [0005]):

"One feature, however, is that certain substances present in the bacterial biomass, among them polysaccharides derived from the bacterial cell wall, lipopolysaccharides and RNA, are difficult to remove without several chromatographic steps, and tend to contaminate the standard DNA preparations. Some of these bacterially derived contaminants are extremely potent effectors of various defence systems of higher eukaryotes, possibly because of their intrinsic function as a signal of bacterial infection. The elimination of these contaminants is a major problem in the manufacture and purification of plasmid DNA."

Further, one of ordinary skill in the art would realize that introduction of bacterial RNA, even in small amounts, might result in some level of expression of bacterial proteins within transfected cells, causing unforeseen and potentially lethal complications. As stated by Cooke et al. (page 298, second paragraph):

"The introduction to patients of plasmid or host nucleic acid sequences that are potentially oncogenic, immunogenic, or that encode antibiotic resistance genes, is of particular concern (Williams et al., 1998). As such, host RNA contamination of a recombinant therapeutic product must be minimised, particularly for therapies that require multiple patient dosing (DiPaolo et al., 1999)."

13. No claims are allowed.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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